IJC
International Journal of Cancer

Rare patients in routine care: Treatment and outcome in advanced papillary renal cell carcinoma in the prospective German clinical RCC-Registry

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Non-clear cell renal cell carcinoma is a very rare malignancy that includes several histological subtypes. Each subtype may need to be addressed separately regarding prognosis and treatment; however, no Phase III clinical trial data exist. Thus, treatment recommendations for patients with non-clear cell metastatic RCC (mRCC) remain unclear. We present first prospective data on choice of first- and second-line treatment in routine practice and outcome of patients with papillary mRCC. From the prospective German clinical cohort study (RCC-Registry), 99 patients with papillary mRCC treated with systemic first-line therapy between December 2007 and May 2017 were included. Prospectively enrolled patients who had started first-line treatment until May 15, 2016, were included into the outcome analyses (n = 82). Treatment was similar to therapies used for clear cell mRCC and consisted of tyrosine kinase inhibitors, mechanistic target of rapamycin inhibitors

Key words: cohort studies, disease management, kidney neoplasms, outcome assessment, outpatients

Abbreviations: CCI: Charlson Comorbidity Index; ccmRCC: clear cell advanced renal cell carcinoma; CI: confidence interval; CPI: checkpoint inhibitors; DCR: disease control rate; IMDC: International mRCC Database Consortium; mRCC: locally advanced or metastatic renal cell carcinoma; MSKCC: Memorial Sloan Kettering Cancer Center; mTOR: mammalian target of rapamycin; ncc(m)RCC: non-clear cell (advanced) renal cell carcinoma; OS: overall survival; PFS: progression-free survival; pmRCC: papillary advanced renal cell carcinoma; RCC: renal cell carcinoma; RCC-Registry: Tumour Registry of Advanced Renal Cell Carcinoma; RCT: randomised controlled trial; TKI: tyrosine kinase inhibitor; VEGF: vascular endothelial growth factor

Conflict of interest: M.S. has received honoraria from Pfizer, GlaxoSmithKline, AVEO, Novartis, Bayer, EUSAPharm, Astellas, Ipsen, Exelixis, Pelloton, EISAI, Bristol-Myers Squibb and Merck Sharp & Dohme. M.S. has received research funding from Pfizer, GlaxoSmithKline, AVEO, Bristol-Myers Squibb, Novartis, Bayer, Roche/Genentech, Immatics, Wilex, Ipsen, Exelixis and EISAI. Furthermore, M.S. has a role of a consultant at Pfizer, GlaxoSmithKline, Novartis, Bayer, Roche, Aveo, EUSAPharm, Astellas, Ipsen, Exelixis, Pelloton, EISAI, Bristol-Myers Squibb and Merck Sharp & Dohme. P.J.G. has received honoraria from Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, Novartis, Pfizer, Sanofi for talks and attendance of expert rounds. N.M. has received support for clinical trials from Bayer, Ipsen, Pfizer, Novartis, Roche and GlaxoSmithKline and honoraria for presentations from Novartis, Bayer, GlaxoSmithKline and Ipsen. Furthermore, N.M. has received travel support from Pfizer, Novartis, Bayer, Roche and Bristol-Myers Squibb and is advisory board member at Novartis, Bayer, GlaxoSmithKline, Ipsen, Pfizer, Bristol-Myers Squibb, Merck Sharp & Dohme. All other authors declare no conflict of interest concerning the topic of this publication.

DOI: 10.1002/ijc.32671
History: Received 27 Mar 2019; Accepted 30 Jul 2019; Online 9 Sep 2019

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and recently checkpoint inhibitors. Median progression-free survival from start of first-line treatment was 5.4 months (95% confidence interval [CI], 4.1–9.2) and median overall survival was 12.0 months (95% CI, 8.1–20.0). At data cutoff, 73% of the patients died, 6% were still observed, 12% were lost to follow-up, and 9% were alive at the end of the individual 3-year observation period. Despite the lack of prospective Phase III evidence in patients with papillary mRCC, our real-world data reveal effectiveness of systemic clear cell mRCC therapy in papillary mRCC. The prognosis seems to be inferior for papillary compared to clear cell mRCC. Further studies are needed to identify drivers of effectiveness of systemic therapy for papillary mRCC.

What's new?

Over the past decade, the treatment landscape for locally advanced or metastatic renal cell carcinoma (mRCC) has dramatically changed. To date, however, guideline recommendations mainly address patients with clear cell mRCC, due to a lack of prospective Phase III evidence for the rarer, non-clear cell mRCC subtypes. This is the first longitudinal, prospective cohort study evaluating treatment and survival of patients with papillary mRCC outside a prospective clinical trial setting. The presented real-world data help bridge the evidence gap by revealing the frequent use and effectiveness of systemic clear cell mRCC therapy in papillary mRCC, with a seemingly inferior prognosis.

Introduction

About 15,100 patients are expected to be diagnosed with renal malignancies in Germany in 2018.[1] Renal cell carcinoma (RCC) comprises more than 90% of renal malignancies.[2] The most common histological subtype is clear cell RCC (70–80%),[2,3] with all other subtypes summarised as non-clear cell RCC (nccRCC) showing distinct molecular and genetic characteristics.[4] Among other rare subtypes, 10–15% of all RCC account for the papillary subset, subdivided into morphologically different Type I and II tumours,[5] and 5% for the chromophobe subtype.[2,6] About 65% of patients with RCC have localised tumours[7]; the remaining ~35% of patients with initially diagnosed locally advanced or metastatic RCC (mRCC) and patients who relapse after initial local therapy (20–30%)[8] usually require systemic treatment.[7] Over the past decade, the systemic treatment for clear cell mRCC (ccmRCC) has markedly changed from a nonspecific cytokine-based immune approach to targeted therapy.[9] The mainstay of therapy is based on blocking vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) signalling pathways. Recently, novel more specific immunotherapy agents such as immune checkpoint inhibitors (CPI), e.g., CTLA-4 inhibitors, were introduced to systemic therapy of mRCC.[7,9,10] Guideline recommendations mainly address patients with ccmRCC, since most of the pivotal clinical trials that have led to the approval of the currently available agents were done in ccmRCC.[11,12] Patients with non-clear cell mRCC (nccmRCC) have largely been excluded from major Phase III randomised controlled trials (RCTs) - except for that of temsirolimus[13] - owing to the heterogeneous histologic nature.[14] Thus, evidence for an optimised treatment approach in patients with nccmRCC having a less favourable prognosis[15] is scarce. Only data from Phase II trials, subgroup analyses from Phase III trials and retrospective studies are currently available.[12,16,17]

In a recent publication, we have shown the changes in treatment reality and effectiveness of treatment in unselected patients with ccmRCC from the German prospective clinical cohort study on mRCC (Tumour Registry of Advanced Renal Cell Carcinoma, RCC-Registry).[18] Filling the gap of knowledge on treatment and outcomes of patients with nccmRCC, we present here comprehensive prospective data from the RCC-Registry on the choice of first-line and second-line treatment between 2007 and 2017, on best response and on progression-free survival (PFS) as well as overall survival (OS) in patients with papillary mRCC (pmRCC) as the most common nccRCC subtype.

Materials and Methods

Data source

The RCC-Registry is an ongoing, open, longitudinal, multicentre, observational, prospective cohort study collecting data on the treatment of patients with documented mRCC. The registry that started in December 2007 was approved by the responsible ethics committee and is registered at ClinicalTrials.gov (NCT00610012). At the time of this analysis, 122 sites (clinics and outpatient centres) located across Germany actively participated and more than 1,500 patients have been enrolled to date. Further details on the methodology of the RCC-Registry have been previously described elsewhere.[18,19]

Cohort definition

At data cutoff of May 15, 2017, n = 1,443 patients with mRCC had been included in the RCC-Registry (Fig. 1). Of all patients with nccmRCC, n = 99 with pmRCC were included into this

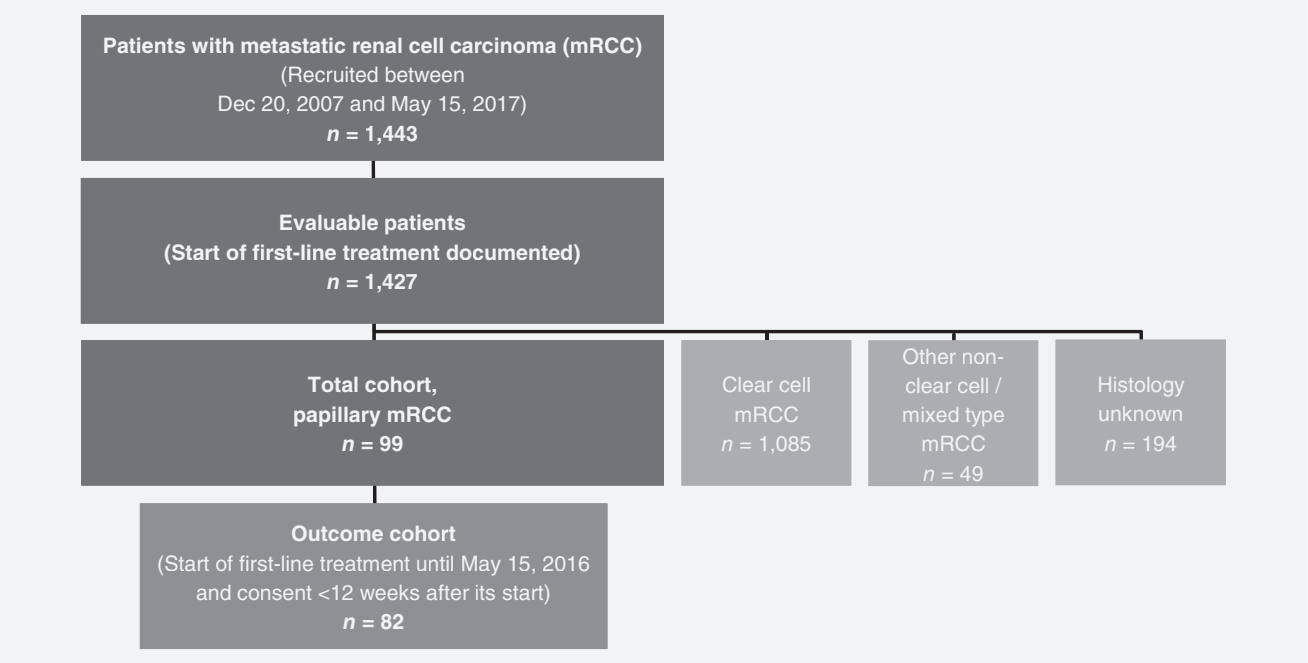

Figure 1. Cohort definition. Number of patients enrolled in the RCC-Registry from December 2007 until May 2017, split up according to the histological subtypes of mRCC. Most of the patients presented with clear cell mRCC, while 7% presented with papillary mRCC comprising our total cohort (n = 99). Thereof, all patients who had started their first-line treatment until May 15, 2016, and had provided written informed consent ‹12 weeks after the start of first-line treatment were included into the outcome analyses (n = 82, outcome cohort).

analysis. Prospectively enrolled patients who had started their first-line treatment until May 15, 2016, and had provided written informed consent no longer than 12 weeks after the beginning of first-line treatment were included into the outcome analyses (n = 82).

Statistical analysis

Time to events was analysed using Kaplan–Meier estimates. OS was defined as the time between the start of first-line treatment until death from any cause. Data of patients alive or lost to follow-up were censored at the last documented contact. PFS was defined as the interval between the start of first-line treatment and date of progression or death prior to the start of second-line treatment. Patients without such a PFS event were censored at either the start of second-line treatment or the last documented contact. All analyses were performed using Dell Statistica, version 13 (Dell, Inc. (2016), software.dell.com) and SAS Statistics for Windows, version 9.4 (Copyright 2002–2012 SAS Institute Inc, Cary, North Carolina).

Data availability

The data that support the findings of our study are available from the corresponding author upon reasonable request.

Results

Patient and tumour characteristics

Patient and tumour characteristics of the total (n = 99) and the outcome cohort (n = 82) presented in Table 1 were comparable. Overall, most patients of the total cohort were male (74%) and median age at the start of first-line treatment was 67 years. Of note, 80% of the patients experienced at least one concomitant disease at the start of therapy; 36% of the patients had comorbidities considered for the Charlson Comorbidity Index (CCI; CCI ≥1). According to the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification,[22] patients were classified into 17% favourable, 61% intermediate and 13% poor risk (9% unknown).

Choice of systemic treatment

Figure 2 shows the used first-line (Fig. 2*a*) and second-line (Fig. 2*b*) treatments between 2007 and 2017.

First-line treatment. Median duration of first-line treatment was 4.6 months (interquartile range, 1.8–9.1). Overall, the most frequently used first-line treatments included sunitinib (39%, 39 of 99 patients), temsirolimus (28%, 28 of 99 patients) and, since 2011–2013, also pazopanib (21%, 11 of 52 patients) which had been approved in 2010 (Fig. 2*a*). While sunitinib was the targeted agent of choice in 2007–2010, there was a decline of sunitinib treatment over time. In contrast, treatment with temsirolimus and pazopanib, respectively, increased over the course of the observation period. A small proportion of patients were treated with one of the other options, especially bevacizumab + interferon-alpha and sorafenib.

Of all prospectively enrolled patients with documented first-line treatment (n = 82), 73% of the patients (n = 60) dropped out of treatment due to progression or death, 9%

Table 1. Patient and tumour characteristics at the start of first-line treatment

Characteristic	Total cohort (n = 99)		Outcome cohort (n = 82)	
	Median	**IQR**	**Median**	**IQR**
Age (years)[1]	66.7	59.6–74.0	68.2	60.6–74.8
	Mean	**SD**	**Mean**	**SD**
BMI (kg/m^2)[1]	26.3	4.8	26.1	4.6
	n	**%**	***n***	**%**
Missing	17	17.2	12	14.6
Sex				
Female	26	26.3	21	25.6
Male	73	73.7	61	74.4
Patients with comorbidity[1]				
Any comorbidity[2]	79	79.8	64	78.0
CCI = 0[3]	63	63.6	52	63.4
CCI ≥1[3]	36	36.4	30	36.6
KPS ‹80%[1]	10	10.1	9	11.0
Unknown	4	4.0	3	3.7
Haemoglobin ‹LLN[1]	41	41.4	38	46.3
Unknown	3	3.0	3	3.7
Calcium ›ULN[1]	1	1.0	1	1.2
Unknown	8	8.1	6	7.3
LDH ›1.5 times ULN[1]	22	22.2	19	23.2
Unknown	9	9.1	6	7.3
Time of initial diagnosis to first-line treatment ‹1 year	59	59.6	46	56.1
Unknown	1	1.0	1	1.2
MSKCC risk category[1,4]				
(0) favourable risk	17	17.2	16	19.5
(1–2) intermediate risk	60	60.6	46	56.1
(3–5) poor risk	13	13.1	12	14.6
Unknown	9	9.1	8	9.8
(Partial) nephrectomy[5]	84	84.8	68	82.9

Abbreviations: BMI, body mass index; IQR, interquartile range; KPS, Karnofsky Performance Status; LDH, lactate dehydrogenase; LLN, lower limit of normal; SD, standard deviation; ULN, upper limit of normal.
[1]At the start of first-line treatment.
[2]At least one comorbidity according to Charlson and/or additional concomitant diseases; mRCC (six points) was not counted as variable.
[3]CCI according to Quan et al.[20,21]
[4]Risk factors according to Motzer et al. 2002.[22]
[5]Prior to systemic first-line treatment.

(n = 7) owing to toxicity and 2% (n = 2) discontinued first-line treatment because of other, not further specified reasons (16% missing, n = 13).

Second-line treatment. Second-line treatment was documented for 60% of the patients (n = 59), while 27% (n = 27) had died prior to receiving second-line treatment. The remainder were either still in first-line treatment (potentially receiving more lines of treatment or had been lost to follow-up after first-line treatment). A broad range of regimens were used for second-line treatment (Fig. 2*b*). Second-line treatment in 2007–2010 was dominated by sunitinib and sorafenib, followed by temsirolimus. Since 2011–2013, the most frequently used second-line treatments included sunitinib, everolimus and pazopanib. The checkpoint inhibitor nivolumab, which had been approved in 2015, was applied to 3 of 16 patients at the time of database cutoff.

Of all prospectively enrolled patients with documented second-line treatment (n = 45), 76% of the patients (n = 34) dropped out of treatment due to progression or death, 9% (n = 4) owing to toxicity and 4% (n = 2) discontinued second-line treatment because of other, not further specified reasons (11% missing, n = 5).

Sequential treatment strategies

Figures 3*a* and 3*b* show the sequential treatment strategies used over time (n = 59). The most frequently applied first-line → second-line sequence over the entire observation period was tyrosine kinase inhibitor (TKI) followed by TKI or by mTOR. There was a trend for a decreasing frequency of the

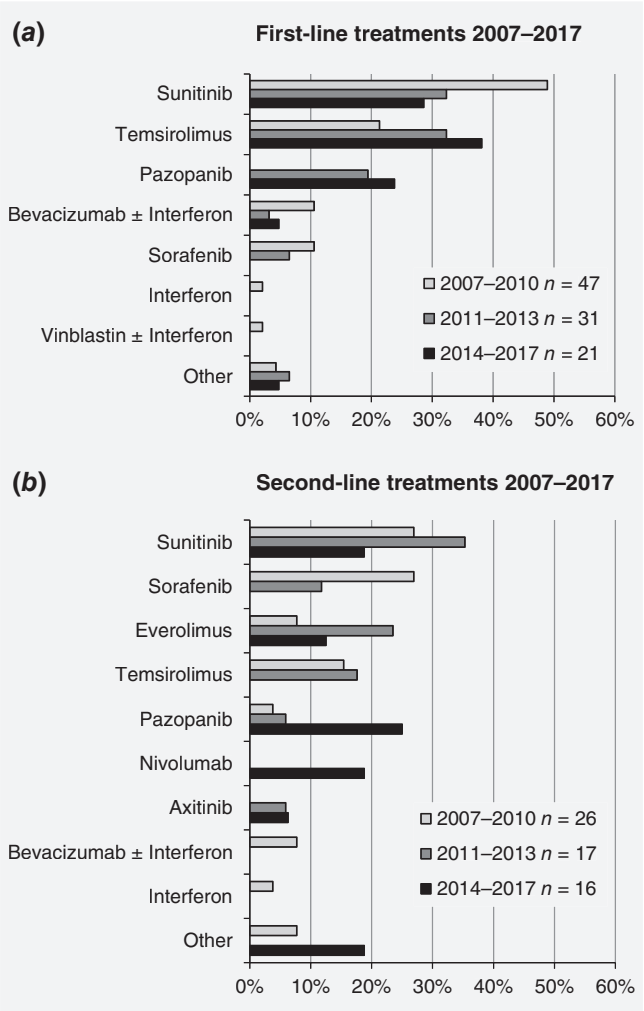

Figure 2. Choice of systemic treatment over time in patients with papillary mRCC. (*a*) First-line treatments from 2007 to 2017 sorted by relative frequency ($n = 99$). (*b*) Second-line treatments from 2007 to 2017 sorted by relative frequency ($n = 59$). Other: Treatments not further specified, e.g., treatments within a randomised blind study.

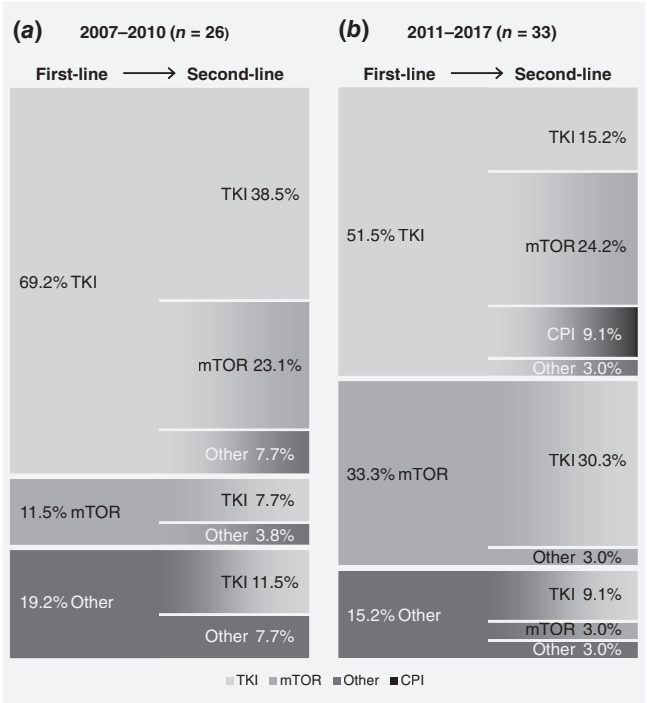

Figure 3. Sequential treatment strategies over time in papillary mRCC. Sequential treatment pattern is presented for all patients whose first- and second-line treatments were documented ($n = 59$). The observation period was split into two subperiods reflecting the approval and introduction of the different targeted second-line treatment strategies (TKI, mTOR, CPI): (*a*) Start of second-line treatment between 2007 and 2010 ($n = 26$). (*b*) Start of second-line treatment between 2011 and 2017 ($n = 33$). Bevacizumab + interferon was included in "Other" strategies. Percentages may not add up to 100% due to rounding.

sequence TKI → TKI over time (from $n = 10$ in 2007–2010 to $n = 5$ in 2011–2017), while the sequence mTOR → TKI tendentially increased (from $n = 2$ in 2007–2010 to $n = 10$ in 2011–2017). Three of 33 patients starting treatment in 2011–2017 received the sequence TKI → CPI (approval of nivolumab in June 2015; Fig. 3*b*). Here, too, care should be taken in interpreting results because of the small proportion of patients analysed.

Best response, PFS and OS

All prospectively enrolled patients were included into the outcome analyses ($n = 82$). With a disease control rate (DCR) covering complete/partial response (17%, $n = 14$) and stable disease (28%, $n = 23$) of 45% (33%, $n = 27$ were unknown/missing; in patients with known best response: 67% DCR), about half of all first-line treatments were successful. Median PFS of patients from the start of first-line treatment was 5.4 months (95% confidence interval [CI], 4.1–9.2; Fig. 4), median OS was 12.0 months (95% CI, 8.1–20.0; Fig. 5). At data cutoff, 73% of the patients with pmRCC had died, 6% were still being observed, 12% were lost to follow-up and 9% were alive at the end of the individual 3-year observation period.

Discussion

The small proportion or exclusion of patients with nccmRCC from pivotal RCTs has resulted in limited evidence on the management of this patient population. To our knowledge, this is the first longitudinal, prospective cohort study evaluating treatment and survival of patients with pmRCC outside a prospective clinical trial setting. We show that drugs mainly investigated for ccmRCC are frequently used in patients with pmRCC. Our data suggest effectiveness of these therapies in patients with pmRCC. However, the prognosis seems to be inferior compared to ccmRCC.

Since only 10–15% of the patients present with pmRCC, the number of patients included into this analysis is rather small compared to more common types of cancer, and

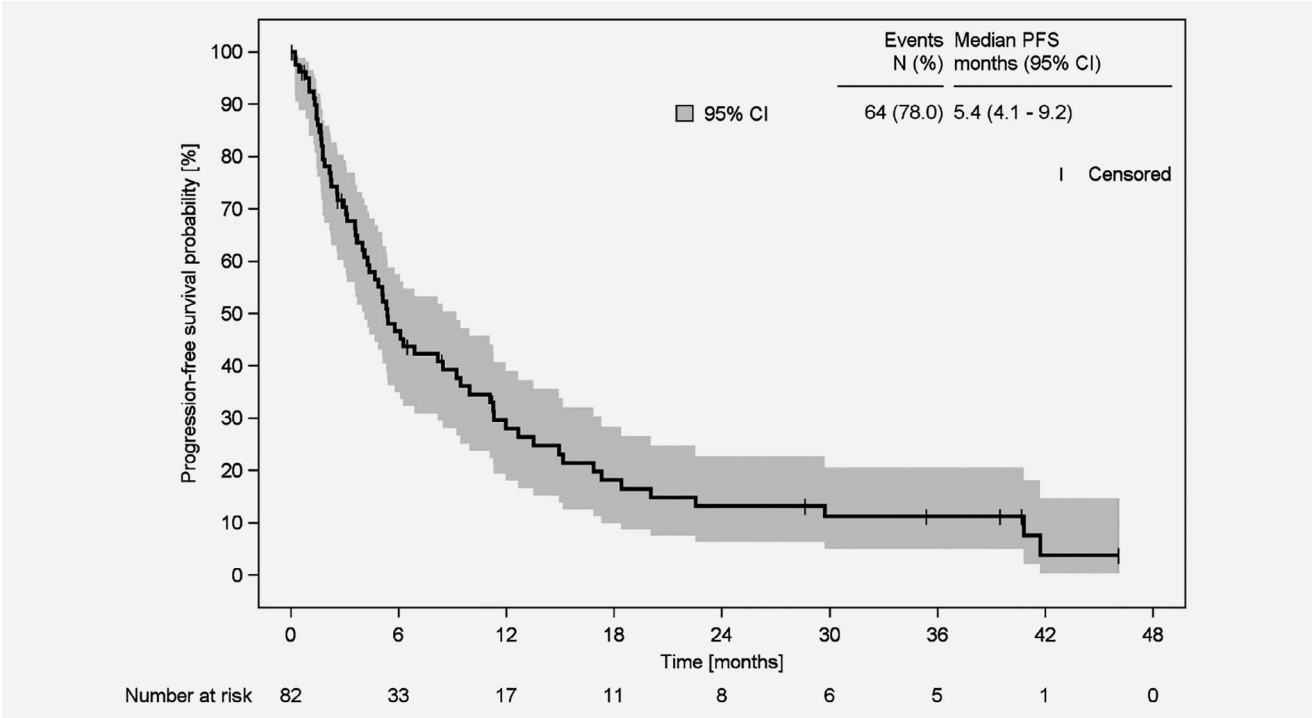

Figure 4. PFS of patients with papillary mRCC since the start of first-line treatment. All prospectively enrolled patients who had started first-line treatment until May 15, 2016, were included (n = 82).

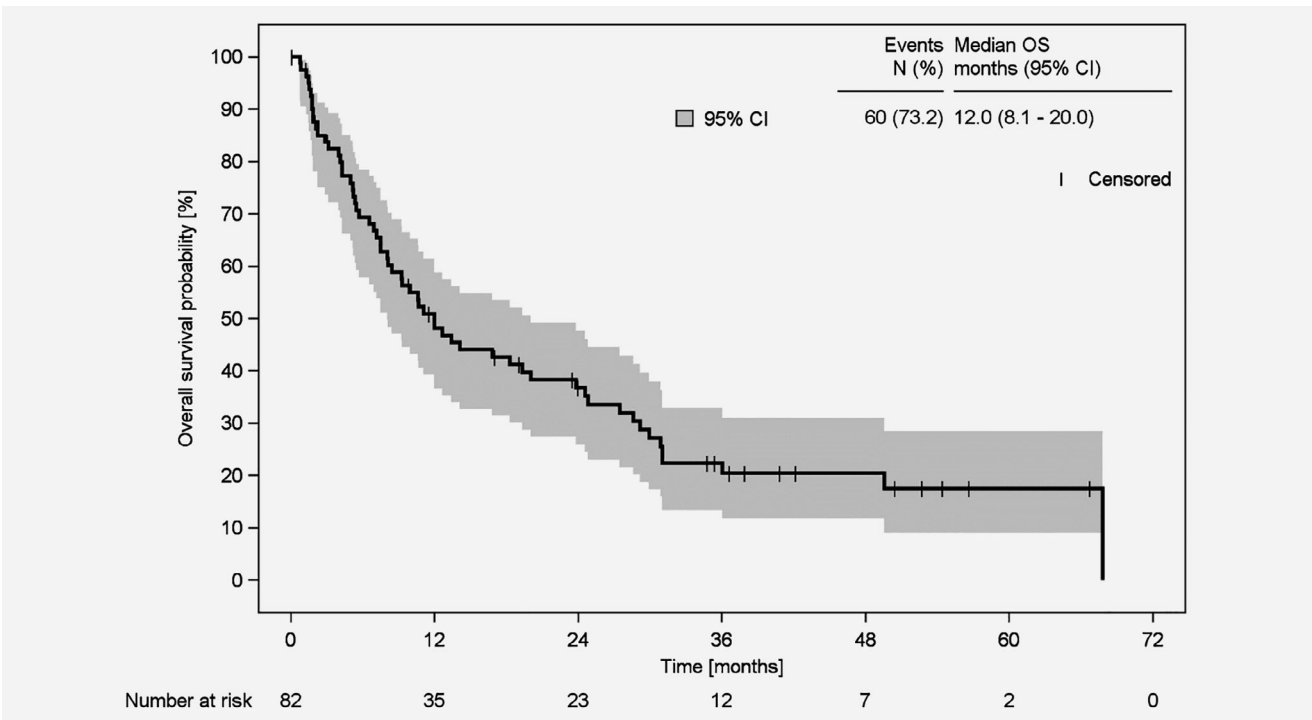

Figure 5. OS of patients with papillary mRCC since the start of first-line treatment. All prospectively enrolled patients who had started first-line treatment until May 15, 2016, were included (n = 82).

percentages should be interpreted with caution, especially when subgroups of this cohort are analysed. In the RCC-Registry, the tumour assessment is not performed according to the Response Evaluation Criteria in Solid Tumours used in clinical trials, and it is not specified when, how often and according to which criteria the treating physician monitors the course of the disease. Apart from that, the recommended interval for restaging under systemic therapy in Germany is 3 months. Thus, the PFS data presented here should be considered the best clinical approximation and might differ from the PFS determined in clinical trials. Strengths of this project are the prospective, longitudinal data collection and the participation of physicians all over Germany recruiting into a large study cohort that allows the analysis of smaller subsets of patients, such as the pmRCC population.

Seven percent of the patients who had been recruited into the RCC-Registry presented with pmRCC which roughly corresponds to the 10–15% usually reported for this histological subtype referring to all RCC including localised disease.[2,6] Each RCC subtype may need to be addressed separately in terms of prognosis and treatment, as subtypes differ in molecular and genetic characteristics.[23,24] Landmark trials have largely focused on ccmRCC, and patients with nccmRCC are generally excluded owing to the smaller proportion and heterogeneous histological subtypes. The Phase III study of temsirolimus carried out in 2007 included the largest subgroup of patients with nccmRCC (20%, $n = 124$) that has been analysed in a Phase III RCT of targeted agents so far.[13]

Here, we present first prospective data on treatment and survival of patients with pmRCC in routine practice. Our data reveal that patients with pmRCC have been treated with the same strategies used for patients with ccmRCC.[18] Overall, the most frequently applied first-line treatments between 2007 and 2017 were sunitinib, temsirolimus and, since 2011–2013, also pazopanib. Sunitinib was the targeted agent of choice in 2007–2010, which is similar to the results reported from a retrospective study of the International mRCC Database Consortium (IMDC) that has aimed to apply the IMDC prognostic model in patients with nccmRCC ($n = 252$; of these, 60% with pmRCC).[25] In our study, more than 90% of the patients with nccmRCC who were treated at 20 international academic (cancer) centres between 2003 and 2012 received a TKI in first-line treatment, with sunitinib being the most common therapy (72%). Although more patients from the IMDC study were classified into poor risk than patients from the RCC-Registry (30% according to the IMDC criteria[25] *vs.* 13% according to the MSKCC criteria), temsirolimus was more often used in first-line treatment of patients from the RCC-Registry, with increasing frequencies seen over time, whereas the use of sunitinib decreased. Second-line treatment of patients from the RCC-Registry until 2011–2013 is comparable to that of patients with nccmRCC from the IMDC study, in which TKIs and mTOR inhibitors, respectively, accounted for 50% and 45% of all second-line treatments, with sunitinib, sorafenib, temsirolimus and everolimus being the most frequently used therapies.[25]

Since the data cutoff for this analysis was May 15, 2017, more recently approved drugs for mRCC treatment had been documented for only a few (such as for nivolumab) or for none of the patients with pmRCC (such as for cabozantinib). Recent retrospective data suggest that CPI[26] and cabozantinib[27,28] might be interesting treatment strategies in nccRCC. Further prospective data are warranted, and some clinical trials are ongoing in this field.[29] The follow-up project of the RCC-Registry, the registry platform CARAT (NCT03374267), which was started in December 2017, will give valuable insight into the current and future systemic treatment strategies and their effectiveness in patients with (n)ccmRCC treated in German routine practice.

The median OS we report here (12.0 months; 95% CI, 8.1–20.0) and the DCR for first-line treatment in patients with known best response (67%) are quite similar to those of the pmRCC subgroup from the IMDC study (median OS: 14.0 months; 95% CI, 10.9–17.1; DCR: 66%).[25] This is even more noteworthy as patients with nccmRCC from the IMDC study treated in academic centres were markedly younger, with only 40% aged 60 years or older[25] compared to 75% from the RCC-Registry, and as retrospectively analysed outcome data can be skewed by immortal time bias. In contrast to the patients with nccmRCC, those with ccmRCC had a median OS of 22.3 months in the IMDC study.[25] This is similar to our recently published data on treatment reality and effectiveness of treatment in patients with ccmRCC from the RCC-Registry, which have shown a median OS of 20.4 and 26.2 months for the ccmRCC population and the potentially trial-eligible subgroup, respectively.[18]

Owing to the absence of Phase III data, the best prospective data on targeted treatment of patients with (any type of) nccmRCC are derived from randomised Phase II trials, namely ASPEN,[30] ESPN[31] and RECORD-3,[32] which aimed to evaluate whether TKIs or mTOR inhibitors have been the most effective treatment approach in nccmRCC.[33] There have also been non-randomised Phase II studies, exclusively conducted in patients with pmRCC.[34–36] All studies were rather small, with the highest proportion of patients with nccmRCC included in ASPEN ($n = 108$).[30] Results revealed a trend or superiority in favour of VEGF inhibitors, especially sunitinib, compared to mTOR inhibitors.[4,12,37]

However, current treatments used in mRCC have demonstrated limited efficacy in nccmRCC,[24] particularly compared to ccmRCC.[32] For patients with pmRCC, median PFS ranged from 4.1 to 5.5 months for everolimus,[30,31,36] 5.7 to 8.1 months for sunitinib[30,31,34] and was 9.3 months for the dual MET/VEGF-receptor inhibitor foretinib.[35] Median OS ranged from 14.9 to 21.4 months for everolimus[31,36] and 12.4 to 17.8 months for sunitinib[31,34] (median OS not reached in the study on foretinib[35]). This roughly corresponds to the effectiveness of the treatment revealed by our routine data (median PFS and OS of

5.4 and 12.0 months, respectively, over all treatments), despite a higher median age of this registry cohort (67 years) compared to that of Phase II study patients ranging from 57 to 64 years.[30–32,35,36] Notably, effectiveness of the treatment of patients from the RCC-Registry was most similar to that reported for patients with Subtype II pmRCC from the non-randomised Phase II SUPAP trial on sunitinib (median PFS and OS of 5.5 and 12.4 months, respectively),[34] with similar age and MSKCC risk of RCC-Registry and SUPAP cohort. In our work, we could not analyse pmRCC separately in groups of Type I and II, because data on this subclassification had not been collected. Research has indicated that prognosis might be worse for patients with Type II than for patients with Type I pmRCC.[34,38,39]

In order to meet the demand for Phase III RCTs, which is listed as the preferred option for patients with nccmRCC in guideline recommendations,[12,40] the Phase III study SAVOIR on the safety and effectiveness of the new anticancer medication savolitinib *vs.* sunitinib in patients with MET-driven, unresectable pmRCC is currently underway (NCT03091192, ClinicalTrials.gov).[41] The results of this trial may add valuable information on the optimal treatment of patients with pmRCC, although recruitment of the planned population of 180 patients will be challenging.

Robust evidence supporting specific treatment strategies for patients with nccmRCC remains lacking. This is the first prospective long-term cohort study showing first- and second-line treatment and survival of patients with pmRCC. Treatments approved for ccmRCC (mainly TKIs, mTOR inhibitors and CPIs) are frequently applied in patients with pmRCC. Survival of patients with pmRCC is quite similar to that reported from most of the few existing (retrospective and prospective Phase II) studies on this histological subtype but is inferior compared to that of patients with ccmRCC. Our real-world data help bridge the evidence gap in the treatment of pmRCC and strongly support the need for clinical trials to identify novel targets and to improve outcomes of this patient group.

Conclusions

Despite the lack of prospective Phase III evidence in patients with pmRCC, our data reveal effectiveness of systemic ccmRCC therapy in pmRCC. The prognosis seems to be inferior for pmRCC compared to ccmRCC. Further studies are needed to identify drivers of effectiveness of systemic therapy for pmRCC.

Acknowledgements

The authors thank all patients, physicians and study teams participating in the RCC-Registry. They also thank the Arbeitskreis Klinische Studien in Onkologischen und Hämatologischen Praxen e.V., the Bund der Urologen e.G. as well as the Arbeitsgemeinschaft Internistische Onkologie in der deutschen Krebsgesellschaft e.V. for supporting this registry.

The authors thank Johanna Harde and Dr. med Leonora Houet (iOMEDICO) for critical comments on the manuscript. The authors would like to thank Dr. Anja Kaiser-Osterhues (iOMEDICO) for her support in preparing the manuscript.

The RCC-Registry is designed, managed and analysed by iOMEDICO and has received continuous financial support from Novartis Pharma GmbH and temporary financial support from Bayer Vital GmbH, Glaxo Smith Kline GmbH & Co. KG, Pfizer Pharma GmbH and Roche Pharma AG. None of the funders had any role in study design, data collection and analysis, interpretation of results, decision to publish, or preparation of the manuscript.

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